Genomic DISC1 Disruption in hiPSCs Alters Wnt Signaling and Neural Cell Fate.

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Public Summary:
Genetic and clinical association studies have identified disrupted in schizophrenia 1 (DISC1) as a candidate risk gene for major mental illness. DISC1 is interrupted by a balanced chr(1;11) translocation in a Scottish family in which the translocation predisposes to psychiatric disorders. We investigate the consequences of DISC1 interruption in human neural cells using TALENs or CRISPR-Cas9 to target the DISC1 locus. We show that disruption of DISC1 near the site of the translocation results in decreased DISC1 protein levels because of nonsense-mediated decay of long splice variants. This results in an increased level of canonical Wnt signaling in neural progenitor cells and altered expression of fate markers such as Foxg1 and Tbr2. These gene expression changes are rescued by antagonizing Wnt signaling in a critical developmental window, supporting the hypothesis that DISC1-dependent suppression of basal Wnt signaling influences the distribution of cell types generated during cortical development.

Scientific Abstract:
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